Remarks

Claims 1-53 and 77-81 are pending in the current patent application. Claims 82-84 have been added. Support for new Claims 82-84 may be found in the originally filed specification and do not add any new matter. Claim 52 has been cancelled since the subject matter of Claim 52 has been incorporated into Claim 51. Claim 53 has been amended to be dependent from Claim 51 to provide proper antecedent basis.

Before addressing the current office action on its merits, Applicant would like to point out some inconsistencies in the Office Action Summary. Reference is made to objections to the specification but no objections were found in the office action. In addition, the pending claims were 1-52 and 77-81 and not 1-76.

§103 Rejections

I. Claims 1, 2, 50-53 and 77 were rejected under 35 §103(a) as being obvious over U.S. Patent No. 6,841,549 (Eisai).

Examiner asserts that Eisai's compound of Example 14 "differs from the claims only in that it lacks the 9-heteroaryl feature required." Example 14 is the only example that describes a compound having a heterocycle at the R^4 position. The vast majority of the compounds disclosed in Eisai have a primary amino group at the R^4 position (48 out of the 60 purine examples). Clearly, Eisai teaches that a primary amino group is preferred at the R^4 position and not a heterocycle. Therefore, unlike the assertions of the Examiner, one would not be motivated to choose a heterocycle for the R^4 position.

It is also important to note that the compounds disclosed by Eisai are adenosine A2 antagonists. Unlike the Eisai compounds, the compounds of the present invention are CB-1 antagonists. Nothing in Eisai teaches or suggests how one would design a compound that would bind to a cannabinoid receptor, in particular, a compound that would act as an antagonist at the CB-1 receptor. Contrary to Examiner's assertions, Eisai fails to provide any motivation or teachings to modify their compounds to produce the compounds of the present invention. It is well-established in the pharmaceutical arts that it would be undesirable for a compound to bind to more than one receptor due to potential unwanted side-effects. Therefore, it would be inconsistent and unreasonable to assume that a pharmaceutical chemist would design around an adenosine A2 receptor antagonist in an attempt to identify a CB-1 receptor antagonist that would be useful in the treatment of obesity.

Unlike Examiner's assertion, obesity does not cause diabetes. Type 1 diabetes is present in patients who have little or no endogenous insulin secretory capacity and patients with Type 2 diabetes are characterized by disorders of insulin secretion and insulin resistance. Although weight reduction and increased energy expenditure may help prevent Type 2 diabetes (decrease insulin resistance), one cannot cure Type 2 or Type 1 diabetes with weight loss, nor are all obese people diabetic as implied by the Examiner. See attached reference: Bastaki, S., "Review Diabetes mellitus and its treatment," Int J Diabetes & Metabolism **13**, 111-134 (2005). In fact, some common antidiabetic compounds are known to cause weight gain (e.g., sulphonylureas thiazolidinediones, and meglitinides). Therefore, it is unreasonable to assume that one would even consider an antidiabetic drug when seeking to identify an anti-obesity agent, in particular an anti-obesity agent based on CB-1 receptor antagonism.

Applicant respectfully submits that Examiner has failed to establish a *prima facie* case of obviousness based on the teachings of Eisai and request withdrawal of the rejection.

§112 Rejections

I. Claim 51 was rejected under 35 USC 112, paragraphs 1 and 2, as being indefinite.

Applicant respectfully submits that the amendment of Claim 51 to include the limitations of Claim 52 renders this rejection moot.

Based on the amendments to the Claims and the arguments provided above, Applicant respectfully submits that Claims 1-51, 53, 77-81 and new Claims 82-84 are in condition for allowance.

Respectfully Submitted:

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Arlene K. Musser
Attorney for Applicants
Registration No. 37,895

Pfizer Inc.
Patent Department, MS: 8260-1611
Eastern Point Road
Groton, Connecticut 06340
(860) 715-0871

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Review

Diabetes mellitus and its treatment

Salim Bastaki

Department of Pharmacology, Faculty of Medicine & Health Sciences, United Arab Emirates University, Al Ain United Arab Emirates.

Abstract

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism. It is the most common endocrine disorder and by the year 2010, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Thus, diabetes covers a wide range of heterogeneous diseases. Diabetes mellitus may be categorized into several types but the two major types are type 1 and type 2. Drugs are used primarily to save life and alleviate symptoms. Secondary aims are to prevent long-term diabetic complications and, by eliminating various risk factors, to increase longevity. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM. Oral hypoglycaemic agents include *sulphonylureas, biguanides, alpha glucosidase inhibitors, meglitinide analogues, and thiazolidenediones.* The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and inadequate insulin secretion. They should be prescribed in combination with an appropriate diet and lifestyle changes. Diet and lifestyle strategies are to reduce weight, improve glycaemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes. Diabetes is best controlled either by diet alone and exercise (non-pharmacological), or diet with herbal or oral hypoglycaemic agents or insulin (pharmacological). The main side effects are weight gain and hypoglycaemia with sulfonylureas, gastrointestinal (GI) disturbances with metformin, weight gain, GI disturbances and liver injury with thiazolidinediones, GI disturbances, weight gain and hypersensitivity reactions with meglitinides and flatulence, diarrhoea and abdominal bloating with alpha-glucosidase inhibitors. (Int J Diabetes Metab 13:111-134, 2005)

Key words: *Diabetes mellitus, treatment, insulin, oral hypoglycaemic agents*

Introduction

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both.[1-4] Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism.[1-4] As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy,[5,6] neuropathy,[7,8] nephropathy,[9,10] cardiovascular complications[11,12] and ulceration.[13,14] Thus, diabetes covers a wide range of heterogeneous diseases.

Diabetes is the most common endocrine disorder and by the year 2010, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025.[15-17]

The diagnostic criteria and the classification of diabetes was first put forward by the World Health Organization (WHO) in 1965[18] then by the National Diabetes Data Group (NDDG) in 1979,[19] and this was followed by simplified recommendations by the WHO in 1980.[20] These WHO recommendations were modified slightly in 1985.[21] The latest recommendations have been published by the American Diabetes Association (ADA) in 1997 and by the WHO in 1999. Both groups agree on the recommendations and criteria.[2,22]

According to the ADA recommendation changes in 1997, the fasting glucose concentration should be used in routine screening for diabetes as well as epidemiological studies; the threshold for fasting glucose was changed from 7.8 mmol/L (140 mg/dl) to 7.0 mmol/L (126 mg/dl); however the 2-h glucose criterion remains as = 11.1 mmol/L (200 mg/dL). For the diagnosis of diabetes, at least one criteria must apply:

- Symptoms of diabetes (polyurea, polydipsia, unexplained weight loss, etc) as well as casual plasma glucose concentration = 11.1 mmol/L (200 mg/dL).
- Fasting plasma glucose = 7.0 mmol/L (126 mg/dL), with no caloric intake for at least 8 h.

2-h plasma glucose = 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test (OGTT), with the glucose load containing 75 g anhydrous glucose in water.

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Correspondence to: Dr. Salim Bastaki, Department of Pharmacology, Faculty of Medicine & Health Sciences, United Arab Emirates University, P.O. Box 17666, Al Ain, United Arab Emirates, Tel: +971-3-7137520

The WHO diagnosis and classification of diabetes mellitus (1999) are identical to those of ADA, a fasting glucose = 7.0 mmol/L (126 mg/dl) and /or a 2-h glucose = 11.1 mmol/L (200 mg/dL). The report states that diagnosis should not be based on a single glucose determination but requires confirmatory symptoms or blood/plasma determination. Ideally, therefore, both the 2-h and fasting value should be used. These recommendations contrast with those of ADA Expert Committee which gives primacy to the 'fasting plasma glucose.' The WHO classification includes both clinical stages (normoglycaemia, impaired glucose tolerance/impaired fasting glucose (IGT/IFG), diabetes) and aetiological types of diabetes mellitus, identical to the ADA except that WHO group includes classification formerly known as gestational impaired glucose tolerance (GIGT) and GDM: fasting glucose = 7.0 mmol/L (126 mg/dL) and/or 2-h glucose = 7.8 mmol/L (140 mg/dL) after a 75-g OGTT.

Diabetes mellitus may be categorized into several types but the two major types are type 1 and type 2.[21,23] On the basis of aetiology, the term type 1 and type 2 were widely used to describe IDDM and NIDDM, respectively; other specific types of diabetes and gestational diabetes are given in Table 1. The term juvenile-onset diabetes has sometimes been used for IDDM and maturity-onset for NIDDM.

On the basis of etiology, type 1 is present in patients who have little or no endogenous insulin secretory capacity and who therefore require insulin therapy for survival. The two main forms of clinical type 1 diabetes are type 1a (about 90% of type 1 cases in Europe) which is thought to be due to immunological destruction of pancreatic ß cells resulting in insulin deficiency; and type 1b (idiopathic, about 10% of type 1 diabetes), in which there is no evidence of autoimmunity. Type 1a is characterized by the presence of islet cell antibody (ICA), anti-glutamic acid decarboxylate (anti-GAD), IA-2 or insulin antibodies that identify the autoimmune process with ß-cell destruction.[23,24] Autoimmune diseases such as Grave's disease, Hashimoto's thyroiditis and Addison's disease may be associated with type 1 diabetes mellitus.[24,25] There is no known etiological basis for type 1b diabetes mellitus. Some of these patients have permanent insulinopaenia and are prone to ketoacidosis, but have no evidence of autoimmunity.[26] This form is more prevalent among individuals of African and Asian Origin.[27]

Table 1: Classification of Diabetes

Type 1(1a,1b)	ß-cell destruction with little or no endogenous insulin secretory capacity Autoimmune Idiopathic
Type 2	Ranges from relative insulin deficiency to disorders of insulin secretion and insulin resistance
Other specific types	Genetic defects of ß-cell function Genetic defects in insulin secretion Diseases of the exocrine pancreas Endocrinopathies Drug-induced or chemical induced Infections (congenital rubella, cytomegalovirus and others) Uncommon forms of immune-mediated diabetes Other genetic syndromes sometimes associated with diabetes Gestational diabetes

Type 2 diabetes is the commonest form of diabetes and is characterized by disorders of insulin secretion and insulin resistance.[28] In Western countries the disease affects up to 7% of the population.[29,30] Globally, it affects 5-7% of the world's population.[15,16,30] This prevalence is underestimated because many cases, perhaps 50% in some population, remain undiagnosed. The prevalence of type 2 diabetes varies considerably throughout the world, ranging from <1% in certain population of the developing countries for example rural Melanesians in Papua New Guinea, and rural Chinese, to over 50% in the Pima Indians of Arizona.[31] There is a higher incidence of type 2 diabetes in urban than in rural areas.[16,31,32] Its incidence is associated with population whose lifestyle has changed from traditional patterns to a modern "Westernized" model.[33]. The classical example include the Pima Indians, Chinese who moved to Mauritius and Japanese who emigrated to Hawaii.[29,33-35] Traditionally, type 2 diabetes is common in individuals over the age of 40. It is often associated with obesity, decreased physical activity and heredity.[36,37] Recent data from several countries show that type 2 diabetes is increasingly becoming a problem among adolescents and even children.[38,39]. In some countries, childhood diabetes type 2 is more common than type 1.[40] The disease is usually controlled through dietary therapy, exercise and hypoglycaemic agents.[41,42]

Gestational Diabetes (GD) *mellitus* refers to the onset or initial recognition of glucose intolerance during pregnancy, usually in the second or third trimester.[43] It occurs in about 4% of all pregnancies. Patients with GD have a 30% to 50% chance of developing DM, usually type 2 DM.

Other types include genetic defects of the pancreatic ß cell or in insulin action pathways (insulin receptor mutations or post-receptor defects)[44] as well as disease of the exocrine pancreas (e.g., Pancreatitis, pancreatic reaction, or cystic fibrosis) are less common causes of DM.[45] Endocrinopathies producing insulin counterregulatory hormones excess (e.g., Cushing's syndrome, acromegaly) may result in DM.[45] Certain drugs like glucocorticoids, pentamidine, niacin, and a-interferon may also lead to DM[46]

Among several monogenic forms of DM which have been identified, maturity-onset diabetes of the young (MODY) is a familial form of NIDDM with autosomal-dominant inheritance, which usually develops in childhood, adolescence or young adulthood, and presents primarily insulin-secretion defects.[44] MODY is not a single entity, but

involves genetic, metabolic, and clinical heterogeneity. Mutations in six genes cause most cases of MODY (MODY 1 - MODY 6).[47-52] The prevalence of MODY is unknown but about 2-5% of patients with type 2 diabetes may in fact have MODY.[53]

Symptoms

Symptoms are similar in both types of diabetes but they vary in their intensity. Symptoms develop more rapidly in type 1 diabetes and more typical. The symptoms include polyurea, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision, and candidiasis.[1] Long-standing type 1 DM patients are susceptible to microvascular complications;[5-10] and macrovascular disease (coronary artery, heart, and peripheral vascular diseases).[11,12]

Symptoms in type 2 DM are similar but insidious in onset. Most cases are diagnosed because of complications or incidentally. Type 2 DM caries a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidaemia and obesity.[11,12,36,37] Most patients with type 2 diabetes die from cardiovascular complications and end-stage renal disease.[9-12] Geographical differences exists in both the magnitude of these problems and their relative contributions to overall morbidity and mortality.[34,35]

Prevention

Insulin replacement therapy is the mainstay of treatment in patient with type 1 diabetes while type 2 diabetes should be regarded as a potentially preventable disease. A study done in Australia Aborigines demonstrated marked improvement in carbohydrate and lipid metabolism in patients with type 2 DM who reverted to a traditional lifestyle.[54] An important large-scale prospective study in China, examined the effects of diet and exercise upon the rate of progression of IGT to diabetes; both the measures, alone or together reduced the progression of the disease by 40% after 6 years.[55] Similar studies done in Sweden also demonstrate the effectiveness of life-style changes in preventing diabetes.[56] More recently, the Finnish Diabetes Prevention Study showed that lifestyle intervention reduced by 58% the risk of subjects with IGT progressing to type 2 diabetes.[57]

Pharmacotherapy

The aim of the treatment is primarily to save life and alleviate symptoms. Secondary aims are to prevent long-term diabetic complications and, by eliminating various risk factors, to increase longevity. The first aim is not difficult to attain and in some elderly patients or those who lack motivation it is the only aim.[58] The care of diabetes on self-management is based on the patient's clinical status and his/her ability to participate in self-care. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM. Oral hypoglycaemic agents include sulphonylureas, biguanides, alpha glucosidase inhibitors and thiazolidenediones.[1] The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and inadequate insulin secretion. They should be prescribed in combination with an appropriate diet and lifestyle changes. Diet and lifestyle strategies are to reduce weight, improve glycaemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes.[59] Diabetes is best controlled either by diet alone and exercise (non-pharmacological), or diet with herbal or oral hypoglycaemic agents or insulin (pharmacological).

Non-pharmacological interventions in the treatment of type 2 Diabetes Mellitus

It has been shown that weight reduction and an increase in daily energy expenditure decrease insulin resistance and increase glucose tolerance.[50] In fact, advice on diet and exercise are an important part of the treatment of type 2 DM. Overweight patients are advised to restrict calorie intake, consume food with low total fat content (especially saturated fat) and high (predominately unrefined) carbohydrate content.

Diet and exercise

Primary prevention is the main aim at preventing diabetes from occurring in susceptible individuals or in general population. Regular physical activity is an important component of the prevention and management of type 2 diabetes mellitus. Prospective cohort studies have shown that increased physical activity, independently of other risk factors, has a protective effect against the development of type 2 diabetes.[60-62] These epidemiological prospective studies demonstrated that various levels of regular physical activity one to several times a week were associated with a decrease incidence of the disease at long-term follow-up (4 and 5 years, respectively) in both men and women of different age groups.[60-62] Type 2 diabetes individuals with moderate or high aerobic fitness have long-term mortality 50-60% lower than diabetic individuals with low cardiorespiratory fitness.

In type 1 diabetics, most studies have not found any benefit from exercise because of the likelihood of type 1 diabetics to consume additional carbohydrates in an effort to prevent hypoglycaemia. Again in type 1 diabetics, hypoglycaemia often develops during light to moderate exercise unless the insulin dose is reduced or extra carbohydrate consumed.[63] In contrast, during and after brief, maximal-intensity exercise, glucose production increases much more than glucose disposal, resulting in hyperglycaemia even in non-diabetic individuals. In type 1 diabetic individuals, insulin levels cannot increase physiologically in response to this hyperglycaemia, so the hyperglycaemia is more marked and prolonged than in non-diabetic subjects.[64,65] Nevertheless, type 1 diabetics who exercise regularly have marked lower long-term morbidity and mortality compared to their sedentary counterparts.[66] For both type 1 and type 2 diabetic patients physical activity is accompanied by gains as well as risks. The physical hazards are generally higher and the metabolic benefits lower in the type 1 than in the type 2 diabetics. On the other hand, for psychological and social reasons, physical activity is desirable because most type 1 diabetic patients are younger than their type 2 counterparts.

Table 2: Fat composition of food high in monounsaturated fatty acids (per portion of 1 Oz/28 g)

	Calories	Total fat (g)	SAFA(g)	MUFA(g)	PUFA (g)
Vegetable oils					
Canola oil	248	28.0	2.0	16.4	8.2
Olive oil	238	27.0	3.6	20.0	2.2
High Oleic (>70%) Safflower oil	240	27.2	1.7	20.4	3.8
High Oleic (>70%) Oil/sunflower	248	28.0	2.8	23.4	1.1
Nuts and seeds *					
Mixed nuts	168	14.6	2.0	8.9	3.1
Almonds	166	14.6	1.4	9.5	3.1
Cashews	163	13.1	2.6	7.7	2.2
Hazelnuts	188	18.8	1.4	14.7	1.8
Macadamia nuts	199	20.9	3.1	16.5	0.4
Peanuts	166	14.1	2.0	7.0	4.4
Peanut butter (smooth), 2 tbsp	190	16.3	3.3	7.8	4.4
Pistachios	172	15.0	1.9	10.1	2.3
Pecans	187	18.3	1.5	11.4	4.5
Sesame butter (tahini) from kernels, 2 tbsp	169	15.2	2.1	5.8	6.7
Sesame seeds	160	13.9	2.0	5.2	6.1
Walnuts (English)	182	17.5	1.6	4.0	11.1
Walnuts (black)	172	16.0	1.0	3.6	10.6
Fruits					
Avocado, raw	45	4.3	0.7	2.7	0.5
Olives	32	3.0	0.4	2.2	0.3

*All nuts and seeds are dry roasted. MUFA, monounsaturated fatty acids; PUFA polyunsaturated fatty acids; SFA, Saturated fatty acids; Source: United States Department of Agriculture (USDA) Nutrient Database for Standard Reference. The United States Department of Agriculture website is http://www.nal.usda.gov/fnic.cgi-bin/nut_search.pl.

Dietary and lifestyle modifications are the mainstay of treatment and management for type 2 diabetes. The majority of people with type 2 diabetes are overweight and usually have other metabolic disorders of the insulin resistance syndrome, so the major aims of dietary and lifestyle changes are to reduce weight, improve glycaemic control and reduce the risk of coronary heart disease (CHD), which accounts for 70% to 80% of deaths among those with diabetes.[59] Even modest weight reduction is associated with a reduction in insulin resistance, a reduction in hepatic glucose production, and perhaps, an improved islet ß-cell function.[67] In type I diabetes mellitus the role of diet is two-fold: first, to help minimize the short-term fluctuation in blood glucose; second, to reduce the risk of long-term complications by obtaining optimal glycaemic control and satisfactory levels of blood lipids. In relation to choices about the types of food for those with type 2 and type 1 diabetes, dietary advice is similar and the major principles remain the same for the entire population who are at risk of CHD.

Fat

In most Western diets, and for that matter many Gulf countries, fat provides 36-40% of total energy and saturated fatty acids (SAFA) 13-18%. Restriction of SAFA and *trans* isomers of unsaturated fatty acids is almost universal.[68] Fat is the most energy-rich of all nutrients and reduction of fat intake helps to reduce total energy intake, which is important for many people with type 2 diabetes and some with type 1 diabetes. Populations consuming a low saturated fat diet have lower incidence and mortality from CHD compared with those living in countries with a high intake of saturated fat and reduced saturated fat intake is associated with reduced levels of low-density lipoprotein (LDL)-cholesterol. Recent evidence suggests that the *trans* isomers of unsaturated fatty acids have a similar adverse effect to that of saturated fatty acids on LDL.[69,70] and, in addition lower high-density lipoprotein (HDL)[70] and an increase lipoprotein (a), Lp(a), which may further contribute to the lipoprotein-mediated CHD.[71] It is for all these reasons that restriction of saturated and *trans* unsaturated fatty acids to 10% or less of total energy has been advised. In numerous studies, substituting vegetable oils rich in n-6 polyunsaturated fatty acids (PUFA)(chiefly linoleic acid) for saturated fat may help to reduce LDL-cholesterol, but in moderate quantities.[72] Debate persists regarding *n*-3 PUFA [eicosapentaenoic (EPA) and docosahexaenoic acids (DHA)], derived from fish oils, which can help to reduce triglycerides and VLDL, as well as reduce the risk of thrombosis as a result of reduced platelet aggregation.[73] Doubt about its effect arose from other investigators who found a variable effect on LDL level[74] and that appropriate ratio of *n*-2 to *n*-6 unsaturated fatty acids has yet to be established.

There is substantial evidence for the benefits of monounsaturated fatty acids (MUFA) with a *cis* configuration (principally oleic acid from olive oil and rapeseed oil derivative, canola)(Table 2). They appear not only to decrease SAFA but also to decrease LDL-cholesterol, increase HDL-cholesterol and may also have antioxidant properties that reduce oxidizability of LDL. Diets high in MUFA are associated with improved peripheral insulin sensitivity and improved glycaemic control.[75] An advantage is that a fairly wide range of intake is considered acceptable. Several non-animal sources of monounsaturated fat including canola oils and nuts are also good sources of polyunsaturated fat [Table 2 and Table 6 in International Textbook of Diabetes Mellitus, Dietary Management in Europe and North America].[77]

Carbohydrates, fiber and glycaemic index

By tradition most of the recommendations for people with diabetes were low carbohydrate diets. More emphasis were placed on the use of complex carbohydrates or starches and the avoidance of simple carbohydrates or sugars on the belief that simple sugars would be digested and absorbed much more quickly. It is now widely accepted that this was unnecessary and indeed undesirable when associated with high consumption of SAFA.[78] It is acceptable for the carbohydrate to be at a higher level provided that the food eaten is rich in soluble fiber and have a low *glycaemic index* (GI) (Table 3).

The concept of *glycaemic index* to rank foods was developed by Jenkins and coworkers[79] based on the increase in blood glucose levels after the ingestion of 50 g of carbohydrate from a test food, compared to a standard amount (50 g) of reference. The GI depends largely on the rate of digestion and rapidity of absorption of carbohydrate.[80] Controlled studies have shown that increasing carbohydrate to the recommended level, by increasing the intake of foods high in soluble fiber (legumes, lentils, some fruits, oats and barley), digestion is much slower and have lower GI values. An intake of 40 g per day of dietary fiber is ideal. Such foods can also produce an appreciable improvement in glycaemic control and a reduction in LDL-cholesterol, without an increase in triglycerides or a reduction in the ratio of HDL to LDL (See table 3 in ref 77). Regular consumption of guar, pectin and other soluble fibers by Jenkins' group[79] has proved beyond doubt that such foods have improved glycaemic control and lower cholesterol levels[81] which was further substantiated by a Finnish Study.[82]

The GI value of food is not the only determinant as to the amount of carbohydrate in food but includes *glycaemic load* (GL) which has been developed to include both the quality and quantity of the carbohydrates consumed.[83] Each unit of dietary GL represents the equivalent glycaemic effect of 1 g of carbohydrate from white bread, which is used as the reference food [See table 3 in reference 76 for GI and GL of selected common foods]. Foods with high GI values include low-amylose white rice, baked potatoes and corn flakes breakfast cereal have the highest GL values.[84] Some foods have high GI values which include carrots and watermelon,

Table 3: Glycaemic index (GI) and glycaemic load (GL) of selected common foods

Food Item	GI (white bread =100)	Serving size	Carbohydrate per serving (g)	GL Per serving (g)
White rice, low-amylose	125	1 cup	53	67
Baked potatoes	121	1	51	61
Corn flakes breakfast cereal	119	1 cup	24	29
Jelly Beans	114	1 oz	26	30
Doughnut	108	1	23	25
Waffle	108	2	31	66
French fries	107	4 oz	35	37
Graham cookies	105	2	11	23
Honey	104	1 tbsp	17	18
Bagel	102	1	38	39
Watermelon	102	1 slice	17	17
Carrots	101	½ cup	8	8
White bread	101	1 slice	12	12
Wheat bread	98	1 slice	12	12
Sucrose	92	1 tsp	4	4
Raisins	91	1 oz	22	20
Ice cream	87	½ cup	16	14
White rice high-amylose	84	1 cup	45	37
Orange juice	81	6 oz	20	16
Cake	80	1 piece	36	29
Brown rice	78	1 cup	45	35
Popcorn	78	1 cup	6	5
Sweet corn	78	½ cup	16	12
Sweet potato	77	1	25	19
Banana	75	1	27	20
Baked beans	68	½ cup	27	18
Parboiled rice	67	1 cup	43	29
Grapes	61	½ cup	14	9
Orange	61	1	16	10
All-bran breakfast cereal	60	½ cup	23	14
Apple juice	58	6 oz	22	13
Spaghetti	58	1 cup	40	23
Apple	51	1	21	11
Chickpeas	47	1 cup	45	21
Lentils	40	1 cup	40	16
Whole milk	38	1 cup	12	5
Kidney beans	38	1 cup	39	15
Grapefruit	36	0.5	10	2
Fructose	33	2 tbsp	31	10
Cherries	31	1 cup	24	7
Peanuts	20	1 oz	5	1

but their GL values are low because these foods provide only a small amount of carbohydrate. Thus GL values may be biologically more relevant than the individual GI values for the reason that they take into account both the quality and quantity of carbohydrates. A study[85] had shown the positive association with fasting plasma triglycerides and the inverse association with HDL appeared to be stronger for dietary GL than for GI. Overweight and obese individuals are much more affected by GL than lean individuals and several large cohort studies have found a positive association between dietary GL and the incidence of type 2 diabetes and CHD.[83]

Sugars and sweeteners

Ranges of non-nutritive sweeteners (including saccharin, aspartame, cyclamate, acesulphame K) are available for

Table 4: Insulin preparations and their properties

Type	Properties (action in hours)		
Rapid	*Onset*	*Peak*	*Duration*
Regular soluble (Crystalline)	0.5-0.7	1.5-4	5-8
Lispro	0.25	0.5-1.5	2-5
Intermediate			
NPH (isophane)	1-2	6-12	18-24
Lente	1-2	6-12	18-24
Slow			
Ultralente	4-6	16-18	20-36
Protamine zinc	4-6	14-20	24-36
Glargine	2-5	5-24	18-24

diabetics and may be useful if added to drinks and cooking. Though aspartame is a dipeptide, it is intensely sweet and very little quantities are required to make food and drinks palatable. All these sweeteners provide a useful means of reducing energy intake. Studies have also shown that under certain circumstances, mono- and disaccharides do not deteriorate glycaemic control or elevate lipid levels [See table 4 under reference 77].[86] Example of such sweeteners are naturally occurring fructose and sorbitol which has been widely recommended for diabetics in the past. However, fructose may increase fasting triglycerides and VLDL, and can cause gastrointestinal disturbances when taken in large amounts and can also cause protein fructosylation.[87] Though they have no advantages over sucrose, moderate intake (maximum of 50 g/day) does not appear to have adverse gastrointestinal or metabolic effects. The use of oligosaccharides is increasing in many countries mainly as a component of functional foods. It has been recommended that sucrose plus other added sugars provide no more than 10% of total energy requirement. This amount was further modified by WHO which suggests that total sugars should provide less than 10% of total energy.

Dietary proteins

Evidence suggests that reducing protein intake to the levels recommended by WHO (0.6 g/kg/day as a safe intake) can reduce albuminuria and improve renal hemodynamics in type 1 diabetes patients with incipient and established nephropathy.[88,89] Such diets do not worsen blood glucose levels[90] and protein undernutrition does not occur in the long term.[91] Though evidence is lacking regarding the benefits of partial or total substitution of animal protein by vegetable protein to reduce proteinuria, vegetable proteins are generally less bioavailable, and more vegetarian-type diets may allow more overall intake in those with early nephropathy.[92] While no confirmation exists of the early suggestions that a high-protein diet contributes to the pathogenesis of early diabetic nephropathy, there is certainly no need for a high protein diet among people with diabetes in general.

Micronutrients: vitamins and minerals

Micronutrients have at one time or the other been the subject of interest in diabetes, in particular chromium, zinc, and magnesium, there is little evidence that those with diabetes have different requirements for vitamins and minerals than those who do not have diabetes.[93] Nevertheless, because of the increased frequency of hypertension and cardiovascular (CV) risks in diabetes, diabetic patients should be advised to restrict sodium intake to 6 g/day or 3 g/day or less if suffering from moderately high blood pressure.[94] Increased potassium intake and sometimes additional supplementation is particularly important when those with diabetes are treated with thiazide and loop-acting diuretics. Though epidemiological evidence exists about the protective effects of antioxidant nutrients (e.g. tocopherols, carotenoids, vitamin C, flavenoids) against CHD and certain cancers in non-diabetic individuals, recent evidence has shown conclusively that supplementation of vitamin E, C, and ß-carotene at least has no impact on CV outcomes.[95]

Folic acid

There is a reduction of CHD[96] among populations who consume diet high in folate and vitamin B_6, probably through reducing plasma homocysteine levels. Hyperhomocysteinaemia is common among diabetic patients and it may contribute to the accelerated risk of artherosclerosis and cardiovascular disease (CVD).[97] It is generally agreed that adequate folate intake is important in diabetic patients. The recommended dietary allowance (RDA) for folic acid was doubled in 1998 to 400 µg per day compared to the previous RDA in 1989.

Alcohol

There is evidence, in people who do not have diabetes, that modest intake of alcohol, especially wine, reduces CV risk because of a beneficial effect on HDL-cholesterol, reduced coagulability (reduced platelet aggregation, decreased fibrinogen, increased tissue plasminogen activator (t-PA), decreased plasminogen activator inhibitor type 1) and reduced lipid oxidation.[98] In diabetics, alcohol consumption should be eliminated in those suffering from hypertriglyceridaemia, in those who are overweight and in those with hypertension. Diabetics who do not have the above complications, alcohol consumption should not be discouraged and should be limited to a quantity equal to two glasses of wine per day.[99,100] Initial studies have suggested that wine was most effective in reducing CHD mortality, though prospective cohort studies have shown all alcoholic drinks to have similar protective profiles. These findings led to the current view that it is the alcohol per se rather than to other components of alcohol beverages.[101] Nevertheless, numerous studies have shown that flavenoids and polyphenols from wine have antioxidant and anticoagulant properties.[102]

One of the major risks with alcohol consumption among individuals with diabetes is the potential danger of hypoglycaemia, especially among those who use sulphonylureas. However, in many clinical studies, no alterations in glucose homeostasis were observed when moderate alcohol is consumed with meals.[103]

Cigarette smoking

Cigarette smoking markedly increases the risk of CHD in diabetes. In one study,[104] compared to those who had never

smoked, the relative risk (RR) for CHD across categories of smoking was 1.21 for past smokers, 1.66 for current smokers of 1-14 cigarettes/day and 2.68 for current smokers with more than 15 cigarettes/day. The RR for women who had stopped smoking for more than 10 years was similar to women who had never smoked.[105] Smoking cessation can have an important effect on CHD risk reduction in diabetic patients, and clinical trials in diabetics who lower their cholesterol levels achieved a 25-55% reduction in risk of major CHD events[106], tight blood pressure control achieved 21% reduction in CHD[107] and intensive blood glucose control achieved 16% risk reduction.[108]

Pharmacological interventions in the treatment of type 2 Diabetes Mellitus

Herbal treatment of diabetes

There are several literature reviews by different authors about anti-diabetic herbal agents, but the most informative is the review by Atta-ar-Rahman who has documented more than 300 plant species accepted for their hypoglycaemic properties.[109] This review has classified the plants according to their botanical name, country of origin, parts used and nature of active agents. One such plant is *Momordica charantia* (Linn/Family: Cucurbaceae) whose fruit is known as Karela/corilla, or bitter gourd. This plant is commonly cultivated in India, China, East Africa and Central and South America. Several studies have examined the anti-diabetic potential of bittergourd, both in humans as well as in animals. The first clinical studies into the effect of fresh juice of bittergourd on management of diabetes was by Akhtar.[110] This study suggested that administration of the fresh juices of bittergourd could treat all symptoms of diabetes including polyurea, polydipsia and polyphagia. Urinary excretion of sugar was also reduced and insulin injections were stopped.

Animal studies on the use of *M. charantia* in diabetes have yielded contradictory results. No effect was observed by Karunanayake et al,[112] (streptozotocin-induced diabetic rats) and Rao et al,[112] (non-diabetic animals) and while other studies have reported significant reductions in blood sugar levels after the administration of *M. Charantia* (freshly prepared juice or dried fruit).[113-115] The seed of *M-charantia* also possesses hypoglycaemic and hypolipidaemic potential.[116]

The hypoglycaemic effect of *M-Charantia* could be due to either: 1) depression of key gluconeogenic enzymes or the increase in the levels of glucose transporters and stimulation of glucose uptake in skeletal muscle cells,[117]; 2) or preserving the structure and function of islet ß cell[118], which could result in a significant increase in insulin secretory activity; 3) or reducing xenobiotic metabolism and oxidative stress and increasing cytochromes P450 and tissue specific alterations in glutathione (GSH) expression and glutathione S transferase (GST) activity[119]; 4) or modulating the biotransformation system and having anti-carcinogenic as well as anti-hypertensive effect[120] and could either delay or prevent diabetes-induced neuropathy by acting like antioxidants preventing development of functional abnormalities caused by diabetes.[121] If it can be assumed that animal studies could be extended to man, *M-charantia* administration may be useful as an adjunct therapy in order to reduce the dosage of insulin or oral hypoglycaemic agents in the management of DM and its complications.

Insulin treatment in diabetes mellitus

The introduction of insulin to treat diabetes has saved an estimated 5 million years of life for patients with type 1 diabetes during the year 2000.[122] Considerable progress has been made, in recent years, in the production, formulation and delivery of insulin preparations, as well as the development of insulin treatment regimens which maintains long-term-normoglycaemia, with a low risk of hypoglycaemia.[123,124] The importance of the aim of preventing or slowing the progression of chronic microvascular complications has been conclusively proven during the last decade, in both type 1 and type 2 diabetes.[108,125] Unfortunately, patients treated with insulin have uniformly poorer glycaemic control compared to those treated with other therapies. It is an accepted fact that insulin is the most potent glucose-lowering agent, with hypoglycaemia being the only major dose-limiting factor. Unlike all oral agents that have limited maximum action, insulin has progressively more side effects as the dose is increased.

Insulin therapy should aim to mimic nature, which is remarkably successful both in limiting postprandial hyperglycaemia and preventing hypoglycaemia between meals,[126] but unfortunately pharmacological problems complicate insulin therapy. In the first instance, subcutaneous insulin injection sites drain into the peripheral, not the portal circulation, thus achieving effective portal insulin concentration only at the expense of hyperinsulinaemia in the systemic circulation. Secondly, pharmacokinetic and pharmacodynamic properties of therapeutic insulin preparations, for example, 'short-acting' insulins are absorbed too slowly and last too long to mimic the normal prandial peaks while 'long-acting' preparations do not provide the steady, low concentrations required between meals. In addition, subcutaneous insulin absorption is highly variable, so that glucose-lowering effect of an insulin dose cannot be predicted. Again the site of injection is equally important being faster from the abdomen than the thigh, injecting more deeply or intramuscularly or by warming, or local massaging or exercise, and from smaller volumes and with less concentrated insulin.[127] Some of the shortcomings have been addressed by the development of insulin analogues

Insulin analogues have an alteration in the amino acid sequence of human insulin, which change the rate of insulin absorption, or some other structural change like being linked to a fatty acid chain, that alters the insulin time action curve.[128] Regular insulin is modified to result in the various short-acting insulin analogies: insulin lispro (Humalog), insulin aspart (Novolog) and insulin glulisine (Apidra); intermediate (Isophane, Lente) long-acting analogues: insulin glargine and insulin detemir.

Many insulin preparations are available and are grouped according to their duration of action: a rapid-acting

formulation to cover meals, intermediate and longer-acting preparations to provide steady (background) basal levels between meals and overnight. Insulin is prepared either from human, or porcine, or bovine or a mixture of bovine and porcine (Table 4). Human insulin (Humulin, Novolin) is now widely available prepared by recombinant DNA techniques. The physicochemical properties of human, porcine and bovine insulins differ owing to their different amino acid sequences. Human insulin is more soluble than porcine insulin in aqueous solutions. It is supplied at neutral pH to make it more stable. Insulin is the mainstay for treatment of virtually all type 1 DM and many type 2 DM patients. Insulin may be administered intravenously (IV), or intramuscularly (IM); however for long-term treatment, subcutaneous (SC) route is preferred.

Short- and rapid-acting insulin preparations: have the most rapid onset of action but the shortest duration. Short-acting insulin (i.e. regular or soluble) usually should be injected 30 to 45 min before meals.[129] Regular insulin may also be given IV or IM. After IV injection, there is a rapid fall in blood glucose concentration within 30-45 (5-15 min for lispro, aspart and glulisine insulins), reaches its peak in 1.5 to 4 hours (30-90 min for Lispro, Aspart and Glulisine) and the duration of its action is 5-8 hours (2-5 hours for Lispro, Aspart and Glulisine). Intravenous infusions of insulin are useful in patients with ketoacidosis or during the perioperative period, during labour and delivery, and in intensive care situations. Regular insulin is present in solution for injection as a hexamer and to be efficiently absorbed into the circulation the insulin hexamer must dissociate into dimmers or monomers. It is this dissociation process that takes 30-60 min that determines the onset and ultimately the time action curve of regular insulin. Unlike regular insulin, the insulin analogues (Lispro, Aspart and Glulisine) dissociate into monomers almost instantaneously following injection. This property results in rapid absorption and shorter duration of action compared to regular insulin.[130] Lispro has two advantages over regular insulin: first, the prevalence of hypoglycaemia is reduced by 20% to 30 %; second, glucose control, as assessed by haemoglobin A_{1c} is modestly but significantly improved (0.3% to 0.5%). Aspart insulin and Glulisine insulins are similar to Lispro.

Several short-acting human regular insulin (dry powder or liquid suspension) preparations are available as inhalations and when delivered have an onset and peak action time similar to that of a rapid-acting insulin but a duration of action slightly longer that that of the currently available rapid-acting insulin analogues.

Intermediate-acting insulin

When given by subcutaneous injection, intermediate-acting insulin preparations have an onset of action of approximately 1-2 hours, a maximal effect at 6-12 hours and duration of 18-24 hours[131] (Table 4). Intermediate-acting insulins are formulated to dissolve more gradually when administered subcutaneously, thus their duration of action is much longer. The two preparations most frequently used are *neutral protamine Hagedon* (NPH) insulin, (isophane insulin suspension) and *lente insulin* (insulin zinc suspension). NPH insulin is a suspension of insulin in a complex with zinc and protamine in a phosphate buffer. Lente insulin is a mixture of crystallized (ultralente) and amorphous (semilente) insulins in acetate buffer, which minimizes the solubility of insulin. NPH and lente insulins exhibit similar pharmacokinetic and pharmacodynamic properties with regards to glucose-lowering action which peak 4-6 hours after subcutaneous injection and then wane over 18-24 hours. Therefore, these insulins are particularly likely to cause nocturnal hypoglycaemia if they are injected before the evening meal, whether separately or in a premixed preparation.[132] Therefore it is preferable to give intermediate-acting insulin preparations at bedtime to help to normalize fasting blood glucose, especially in type 2 DM.[133] The injections are either given once (in the elderly) or twice a day. The introduction of intermediate-acting insulin preparations resulted in reduction of the frequencies of multiple injections of regular insulin. Regular and NPH insulin could be mixed together in the same syringe. NPH does not retard the action of regular insulin when the two are mixed together[134] compared to lente insulin where some of the lente insulin may form a complex with the protamine or ZN^{2+} after several hours and delay the absorption of the fast-acting insulin.[135]

Long-acting insulin preparations

Ultralente insulin (extended insulin zinc suspension) and *protamine zinc insulin* suspension are long-acting insulins; they have a very slow onset and a prolonged, relatively 'flat' peak of action. Ultralente continues to be classified by many as long-acting insulin (Table 4). Although some insulin is present 24 h after injection, it is not sufficient to provide adequate basal or background insulin coverage. Ultralente insulin has an onset and peak similar to that of intermediate-acting insulin but a bit later or prolonged. Ultralente has a duration that is longer than that of intermediate (prolonged) but not as long as insulin glargine. In most cases it is used twice a day (morning and at bedtime) or in a regimen where ultralente is given at breakfast to provide basal insulin throughout the day and evening, and NPH is given at bedtime to suppress hepatic glucose production overnight. Today this regimen of incorporating ultralente is less often used with other long-acting insulin preparations available. Protamine zinc insulin is rarely used today because of its very unpredictable and prolonged course of action, and is no longer available in the United States.

The only insulin available today that meets most of the characteristics of long-acting insulin is *insulin glargine* (Lantus). Insulin glargine is created by recombinant DNA techniques, resulting in the changes in the amino acid structure of regular insulin and is thus called an insulin analogue. Glargine is a clear solution with a pH of 4.0. Because of its acidic pH it cannot be mixed with currently available short-acting insulin preparations (regular insulin or lispro) that are formulated to a neutral pH. When injected subcutaneously, it shows a prolonged, flat action profile lasting approximately 24 h and can therefore achieve adequate basal levels when injected once daily.[136,137]

Glargine injected at bedtime causes less frequent hypoglycaemia overnight and lower and less variable fasting glucose concentration when compared to NPH insulin, in both adults[138] and children.[139] In some patients there is not adequate basal insulin coverage (determined by glucose going up just before the next glargine injection), and it is advisable to administer rapid-acting insulin with the meal than splitting the insulin glargine into two injections. In instances where glucose control is adequate but does appear to be waning basal insulin coverage, then it is appropriate to split the insulin glargine. Insulin glargine is not approved for use in pregnancy and there is insufficient data in pregnancy to make a recommendation for clinical use at this point.

Addition of a saturated fatty acid to the e amino acid yielded acylated insulin. One such insulin analog, *insulin detemir,* is currently available. Insulin detemir has a fatty acyl chain attached at the B29 lysine amino acid of regular insulin and absence of threonine at B30. The fatty acyl side chain slows the metabolism and removal from the circulation after subcutaneous injection, resulting in a time action that is longer than that of intermediate one but not as long as insulin glargine. Whether insulin detemir is eventually classified clinically as a prolonged-intermediate-acting insulin (usually requiring two injections per day and having a moderate peak) or a long-acting insulin (usually one injection per day with a minimal peak) depends on future clinical trials and clinical experience.

Premixed insulin

Premixed insulin was developed for patient's convenience and for simplicity in ordering and dosage adjustment by the physician. Premixed insulin is available today in one or several ratios of short-acting insulin or rapid-acting insulin (soluble insulin) to intermediate-acting insulin (NPH or a protamine suspension). The premixed insulin formulations, mostly in ratios of 30/70 (soluble/NPH) account for much of the insulin in use but are slowly being joined by the new generations of mixtures of rapid-acting analogues (lispro or aspart) with protamine-retarded counterparts, e.g. lispro/neutral protamine lispro (25/75, 50/50 and 75/25 and aspart/neutral protamine aspart (30/70, 50/50 and 70/30). Conventional premixed insulin preparations are injected twice a day, before breakfast and the evening meal. Despite their popularity, some professionals feel any fixed ratio of short to intermediate insulin does not allow 'fine-tuning' of each insulin component to self-monitoring blood glucose (SMBG) patterns. As yet no direct comparisons of premixed insulin to self-mixing and adjusting each insulin have been done. Clinical experience with premixed insulin has shown that this category of insulin compounds is not appropriate for type 1 diabetes where frequent adjustment to achieve optimal control of blood sugar level is needed. On the other hand, in type 2 diabetes, the benefits of simplicity and ease of adjustment for both patients and provider may outweigh the disadvantage of the inability to fine-tune the doses. Rapid-acting insulin analogues are gradually replacing regular insulin because of improved postprandial glucose control, less hypoglycaemia, and more patient convenience in timing of insulin doses.

Complications of insulin therapy

The most common adverse reactions to insulin are *weight gain* and *hypoglycaemia.*[140,141] Hypoglycaemia may result from an inappropriately large dose, from mismatch between the peak delivery of insulin and food intake or from superimposition of additional factors that increase sensitivity to insulin (adrenal insufficiency, pituitary insufficiency) or that increase insulin-independent glucose uptake (exercise). The more vigorous the attempt to achieve euglycaemia, the more frequent the episodes of hypoglycaemia. In one clinical trial (DCCT), the incidence of hypoglycaemia reactions were three times higher in the intensive insulin therapy group than in the conventional therapy group.[142] Use of physiological insulin regimens combined with education can actually decrease the frequency of hypoglycaemia[143,144] and reduce the risk of hypoglycaemia.[145,146]

Weight gain after starting insulin therapy for uncontrolled diabetes is an inevitable consequence and is the result of increased truncal fat and muscle bulk.[147,148] This is also due to reduced energy losses through glycosuria. In this case physiological insulin regimens can help to minimize weight gain by reducing inappropriate insulinaemia and hypoglycaemia between meals and thus the need for snacks in both adults and children. In type 2 diabetes metformin can help limit weight gain when insulin is started[148] (see metformin later under biguanides).

Insulin allergy and resistance. There has been a dramatic decrease in the incidence of resistance and allergic reactions to insulin with the use of human insulin or highly purified preparations of the hormone. Bovine insulin was especially prone to cause allergic reactions. These reactions still occur as a result of the small amounts of aggregated or denatured insulin in all preparations, to minor contaminants, or because of sensitivity to one of the components added to insulin in its formulation (protamine, Zn^{2+}, phenol, etc.). The most frequent allergic reactions were IgE-mediated local urticaria reaction which are extremely rare nowadays.[149] Skin testing are useful, however many patients exhibit positive reaction to intradermal insulin without experiencing any adverse effect. If allergy persists desensitizing should be attempted and is successful in 50% of the patients.

Lipohypertrophy and lipoatrophy. Atrophy of subcutaneous fat at the site of insulin injection (lipoatrophy) is probably an immune response to insulin from animal sources and is no longer a problem with human insulins. Lipohypertrophy is localized overgrowth of subcutaneous adipose tissue in response to lipogenic and growth-promoting effects of high local insulin concentrations.[150] It is more common in patients taking multiple insulin injections repeatedly in the same site, usually the abdomen. Lipohypertrophy can be avoided by rotating insulin injection sites.

Insulin edema occurs to some degree but disappear spontaneously within several days to a week unless there is underlying cardiac or renal disease. This is attributed to retention of Na+ although increased capillary permeability associated with inadequate metabolic control may also contribute.

Oral hypoglycemic agents: Sulfonylureas

Sulphonylureas are structurally related to sulphenamides and were discovered accidentally, in 1942 when it was noted that some sulphonamides caused hypoglycaemia in experimental animals. These observations were extended, and 1-butyl-3-sulfonylurea (*carbutamide*) became the first clinically useful sulfonylurea for the treatment of diabetes. This compound was later withdrawn because of adverse effects on the bone marrow but led to the discovery of the entire class of sulfonylureas. In the 1950s *tolbutamide* was widely used in type 2 DM and subsequently 20 different agents of this class have been in use worldwide. This was followed by the introduction of biguanides, *phenformin*, which was later withdrawn because of an increase in the frequency of lactic acidosis associated with it use. Later on *metformin* was introduced and this drug has been used extensively in Europe without the side effects of *phenformin*.

It was demonstrated that non-sulfonylurea analogues moiety was not necessary for stimulating insulin secretion. [151,152] The first generation of sulfonylureas includes *tolbutamide, acetohexamide, tolazamide, and chlorpropamide*. A second generation of sulfonylureas has emerged and includes *glibenclamide (glyburide in USA), glipizide, gliclazide, and glimepiride* (Table 5). They are more potent than the earlier agents.

Mechanism of action

Sulfonylureas cause hypoglycemia by stimulating insulin release from pancreatic ß-cells. They bind to sulfonylurea (SUR) receptors on the ß-cell plasma membrane, causing closure of adenosine triphosphate (ATP)-sensitive potassium channels, leading to depolarization of the cell membrane. This in turn opens voltage-gated channels, allowing influx of calcium ions and subsequent secretion of preformed insulin granules. Acute administration of sulfonylureas to type 2 DM patients increases insulin release from the pancreas and also may further increase insulin levels by reducing hepatic clearance of the hormone. Initial studies showed that a functional pancreas was necessary for the hypoglycaemic actions of sulfonylureas.[153] With chronic administration, circulating insulin levels decline to those that existed before treatment. But, despite this reduction in insulin levels, reduced plasma glucose levels are maintained.

Table 5: Classification of oral antidiabetic agents

Sulfonylureas	*Thiazolidinediones*
Acetohexamide	Pioglitazone
Carbutamide	Rosiglitazone
Chlorpropamide	Troglitazone
Glibenclamide	
Glibornuride	*Meglitinides*
Gliclazide	Nateglinide
Glimepiride	Repaglinide
Glipizide	
Gliquidone	Aldose Reductase
Inhibitors	
Glisentide	Epalrestat
Glisolamide	Sorbinil
Glisoxepide	
Glyclopyramide	*Alpha Glucosidase*
	Inhibitors
Glycyclamide	Acarbose
Tolazamide	Miglitol
Tolbutamide	Voglibose
Biguanides	*Miscellaneous*
Buformin	Glybuzole
Metformin	Glymidine
Phenformin	Guar Gum
	Midaglizole

Pharmacokinetics

Though the rates of absorption are different for different sulfonylureas, all are effectively absorbed from the gastrointestinal tract. However, food and hyperglycaemia retards absorption. In general sulfonylureas with short half-lives may be more effective when given 30 min before eating due to the time required to reach optimal concentration in the plasma. The first-generation sulfonylureas vary considerably in their half-lives and extents of metabolism. The half-life of acetohexamide is short, but the drug is reduced to an active compound with a half-life that is similar to those of tolbutamide and tolazamide (4-7 h). Therefore it is necessary to take these drugs in divided daily doses. The short-acting sulfonylureas include glipizide, which has the shortest half-life (1-5 h) and no active metabolites; other sulfonylureas with short half-lives are glibornuride (5-12 h), gliclazide (6-15 h), glimepiride (5-9 h), tolazamide (4-7 h), and tolbutamide (6-12 h), and these have metabolites with little or no activity.[154] Chlorpropamide has the longest elimination half-life (24 to 48 h, or longer in subjects with renal impairment) of all sulfonylureas currently in use, and is very long-acting.[154] Gliquidone has the next longest elimination half-life (24 h), but little is known of its clinical duration of action and the risk of long-lasting hypoglycaemia, mainly because the use of this sulfonylurea has so far been very limited. The second-generation agents are approximately 100 times more potent than those in the first group.[155] Although they have shorter half-lives (3 to 5 h) they are generally given twice daily but it is often possible to give them once daily. Glibenclamide was reported in some studies to have a short elimination half-life of (2-10 h), a recent study has showed that the elimination half-life is rather long (15-20 h).[156] This appears to be the case since the drug has a long duration of action, more widely used, and is implicated in more cases of long-lasting hypoglycaemic episodes than other sulfonylureas.[154,157]

All of the sulfonylureas are metabolized in the liver, and the metabolites are excreted in urine. Chlorpropamide is not completely metabolized, 20% of the drug is excreted unchanged.[154] Thus, sulfonylureas should be administered with caution in patients with either renal or hepatic insufficiency. All sulfonylureas have a low clearance.[154] Some, but not all, sulfonylureas have active metabolites that may depend upon renal function for their elimination.

Adverse reactions

Adverse effects of sulfonylureas are infrequent, occurring in the range of 2-5% for first-generation drugs and perhaps

slightly less often in patients receiving second-generation agents.[158] Most are mild and reversible upon withdrawal. The most common side effect of sulfonylurea is *hypoglycaemia*, which though usually mild to moderate, can cause fatal complication.[159,160] In the United Kingdom Prospective Diabetic Study (UKPDS) group[108] the rates of any hypoglycaemic symptoms were 11% for *chlorpropamide*, 17.7% for *glibenclamide*, 36.5% for *insulin*, and 1.2% for *lifestyle* management. Long-lasting and serious hypoglycaemia occurs more often with long-acting sulfonylureas, such as *glibenclamide* and *chlorpropamide* than with short-acting ones, such as *glipizide* and *tolbutamide*.[160,161] Most patients with severe hypoglycaemia are over the age of 70 and have additional risk factors such as excessive alcohol intake, poor nutrition, impaired renal function and drug interaction.[157] The number of serious cases in the Swiss review were 0.38, 0.34, 0.15, and 0.07 per 1000 treatment –years for *glibenclamide, chlorpropamide, glipizide, and tolbutamide*, respectively.[162]

Avoiding long-acting sulfonylureas, particularly, in patients with predisposing conditions or who are taking potentially interacting drugs can minimize severe sulfonylurea-induced hypoglycaemia. When such cases do occur the patient should be hospitalized and a bolus of 50% glucose should be given intravenously and should be followed by continuous infusion of 10%-20% glucose. Blood glucose should be monitored and maintained at 6-8 mmol/l (110-145 mg/dl). If IV glucose is insufficient, hydrocortisone and /or glucagon administration may be useful. A somatostatin analogue (octreotide) has been shown to reverse sulfonylurea-induced hyperinsulinaemia and hypoglycaemia and has been shown to be very effective in severe and intractable cases of sulfonylurea-induced hypoglycaemia.[163,164]

Weight gain is a frequent complication of sulfonylurea treatment and well-controlled studies have found that the mean yearly increase in body weight was 2.8 kg.[165] This is in contrast to a mean decrease of 1.2 kg that occurred with comparable improvement in glycaemic control by metformin treatment. In UKPDS, patients receiving sulfonylureas had a net increase in weight of 3 kg compared to conventionally treated patients.[166] The weigh gain occurred during the first 3 to 4 years of treatment and then stabilized. Several explanations have been given for the increase in weight associated with sulfonylureas. Improvement in glycaemic control decreases glycosuria and can increase caloric balance if food intake is not sufficiently reduced. Mild *hypoglycaemia* associated with sulfonylureas can manifest itself as hunger and thus increase food intake.

Other effects may include *gastrointestinal disturbances* and *headache*. *Hypersensitivity* reactions are uncommon but may occur in the first 6-8 weeks of therapy and include transient *rashes, fever*, and *jaundice*. Blood disorders are rare, but include thrombocytopenia, agranulocytosis, and aplastic and haemolytic anaemias.

Several drugs interfere with the efficacy of sulfonylureas, particularly the first-generation agents, by influencing their pharmacokinetics or pharmacology or both. Some drugs displace the sulfonylureas from their binding proteins, thereby increasing the free concentration transiently.[160] These include other sulphonamides, clofibrate, discumarol, salicylates, and phenylbutazone. Two of the most important interactions may occur with alcohol and with aspirin, both of which may cause hypoglycaemia.[154,157] About 10-15% of patients on chlorpropamide develop an alcohol-induced flush similar to that caused by disulfiram. Chlorpropamide may also induce hyponatremia by potentiating the effects of antidiuretic hormone on the renal collecting duct,[158] which may occur in about 5% of all patients; it is less frequent with glyburide and glipizide.

Cardiovascular effects

The most frequently debated adverse effect of sulfonylureas is that centered around whether or not treatment with sulfonylureas is associated with increased cardiovascular mortality. This possibility was suggested in 1970 by the University Group Diabetes Program (UGDP) study.[167] Studies have shown that glibenclamide in ordinary antidiabetic doses abolished ischaemic preconditioning[168] while other sulfonylureas such as glimepiride do not adversely affect ischaemic preconditioning.[168] Some studies have shown an increase in mortality risk in patients taking sulfonylureas compared to other treatments[169,170] while others have found no effects on cardiovascular events.[171,172] To avoid this cardiovascular controversy, it is best to use sulfonylureas that have no effects on ischaemic preconditioning.[173]

Therapeutic uses

Sulfonylureas have an important role in the management of type 2 DM patients who cannot achieve proper control with changes in diet alone. However, continued dietary restrictions are essential to maximize the efficacy of sulfonylureas. Some physicians still consider treatment with insulin to be the preferred approach in such patients. When used appropriately, sulfonylureas are safe, particularly the short-acting ones.

Contraindications

Contraindications to the use of these drugs include type 1 DM, pregnancy, lactation, and significant hepatic and renal insufficiency.

Combinations

Combination with other antidiabetic drugs should be considered when combination of strict diet and sulfonylurea treatment fails

- Combining with metformin (see later under biguanides)
- Combining with acarbose which may have a small beneficial effect, but flatulence can be a problem
- Combining with thiazolidinediones for example pioglitazone or rosiglitazone (see later)
- Combining with bedtime isophane insulin but weight gain and hypoglycaemia can occur.

Insulin therapy should be instituted temporarily during illness such as myocardial infarction, coma, infection or trauma. Sulphonylureas should be omitted on the morning of surgery; insulin is often required because of the ensuing hyperglycaemia in these circumstances.

Biguanides

Metformin (Glucophage) and *phenformin* were introduced in 1957 and *buphormin* was introduced in 1958 (Table 5). They were widely used in Europe for treating type 2 diabetes for nearly 20 years. The latter two were withdrawn in many countries in the 1970s because of an association with fatal lactic acidosis.[174] Additionally an increased risk of cardiovascular mortality was seen with oral hypoglycaemic agents compared with insulin.[175] Metformin has a very low rate of lactic acidosis compared with phenformin and has been widely used in Europe, Canada, Middle East and other countries; it became available in the United States in 1995. Metformin given alone or in combination with a sulfonylurea improves glycaemic control and lipid concentrations in patients who respond poorly to diet or to a sulfonylurea alone.[176] Studies have shown that metformin improves insulin resistance in the liver, skeletal muscle, and adipose tissue, a major pathogenic component of type 2 diabetes.[177] It was shown to have efficacy similar to that of sulfonylureas in reducing fasting plasma glucose (FPG) and postprandial glucose concentrations, but caused no weight gain or hypoglycaemia in contrast to sulfonylurea therapy.[178,179]

Mechanism of action

The mechanism of action of metformin is not fully understood. Metformin is antihyperglycaemic, not hypoglycaemic.[177] It does not cause insulin release from the pancreas and does not cause hypoglycaemia, even in large doses.[179] Metformin has no significant effects on the secretion of glucagon, cortisol, growth hormone, or somatostatin. It has been shown to increase peripheral uptake of glucose,[180] and to reduce hepatic glucose output by approximately 20-30% when given orally[181] but not intravenously.[182] Impaired absorption of glucose from the gut has also been suggested as a mechanism of action, but has not been shown to have clinical relevance. Metformin has also been shown to decrease serum triglycerides and fatty acid concentrations[181,183] and slows the rate of lipid oxidation,[181,183] actions that indirectly inhibit gluconeogenesis.

Metformin treatment is associated with statistically and clinically significant reduction in body weight in obese patients with type 2 diabetes. These are independent of its effect on glycaemic control.[184]

Pharmacokinetics

Metformin is mainly absorbed from the small intestine. The drug is stable, does not bind to plasma proteins, and is excreted unchanged in urine. It has a half-life of 2 hours. The maximum daily dose of metformin in the United States is 2.5 g taken in three doses with meals.

Adverse effects

Approximately one-third of patients on metformin will have transient nausea, anorexia or diarrhoea, abdominal discomfort, and metallic taste. These side effects can be minimized by starting with a low dose (500 mg daily) and gradually increasing the dose up to 800-850 mg thrice daily. Intestinal absorption of vitamin B_{12} and folate is often decreased during chronic metformin therapy. Calcium supplements reverse the effect of metformin on vitamin B_{12} absorption.[185] Other adverse effects reported are headache, agitation, dizziness and tiredness.

Lactic acidosis is a rare but serious, potentially fatal metabolic adverse effect in metformin-treated patients and it is estimated to have an incidence of 0.03 per 1000 patient-years.[186] Metformin-associated lactic acidosis occurs in patients with severe renal impairment and renal hypoperfusion.[187] In the event of accumulation, metformin can be removed by dialysis[188] and the mortality rate is about 50%, the prognosis depends on the severity of the underlying conditions.[188] The risk of death is similar to that of hypoglycaemia in sulfonylurea-treated patients.[189]

Contraindications

Metformin is contraindicated in patients with impaired renal, respiratory or hepatic function, cardiac failure, or a history of alcohol abuse.

Uses

Metformin is the drug of first choice in overweight patients in whom strict dieting has failed to control diabetes. It may also be considered as an option in patients who are not overweight. It is also used when diabetes is inadequately controlled with sulfonylurea.

Combination with other glucose-lowering agents

- The combination of metformin with either glyburide or glipizide has been evaluated as both a first-line and a second-line pharmacologic therapy for the management of type 2 diabetes.[176,190] In comparative trials, metformin plus sulfonylurea, either as two tablets administered together or as glyburide/metformin tablets or glipizide/metformin tablets, provides significantly better glycaemic control than either agent used alone.
- Combining with acarbose may have a small beneficial effect, but flatulence can be a problem
- Combining with insulin in type 2 diabetes further improves FPG and reduces insulin dosages by approximately 25-36% in some studies and obviated the need for insulin completely in other studies.[191] Weight gain and hypoglycaemia can be a problem which can be minimized by giving insulin at night.
- Metformin is also available in combination with the thiazolidinediones rosiglitazone or pioglitazone. This combination is preferred to a thiazolidinedione plus sulfonylureas particularly for obese patients.[192] There is sparse information on the efficacy or safety of this combination.

- Combining with repaglinide or nateglinide.

Insulin treatment is almost always required in medical and surgical emergencies; insulin should be substituted before elective surgery (omit metformin the evening before surgery and give insulin if required).

Summary

Metformin is a valuable agent for the treatment of type 2 diabetes. Unlike other oral antidiabetic agents, metformin has been shown to provide additional benefits in reducing macrovascular complications of type 2 diabetes in overweight patients, including any diabetes-related endpoint, all-cause mortality, and stroke.[193] Metformin also improves serum lipoprotein parameters, reduces body weight, and stimulates fibrinolysis, factors that likely contribute to reduced adverse macrovascular outcomes that are exclusive to metformin.

Metformin can be administered with insulin and other oral antihyperglycaemic agents. Improvements in glycaemic parameters are additive when metformin is combined with other agents. The dose of insulin can be reduced with metformin therapy and can be obviated altogether. Availability of the combination tablets (with glyburide, glipizide or rosiglitazone) and an extended-release formulation allows for simple dosage regimens. This is particularly attractive among population of patients with having comorbidities and requiring multiple medications.

Thiazolidinediones

Thiazolidinediones (TZDs) are chemically and functionally unrelated to the other classes of oral antidiabetic agents. A thiazolidine-2,4-dione structure is common to all agents. Two compounds in this class are currently in use. Rosiglitazone (Avandia) and pioglitazone (Actos) are the two thiazolidinediones in use.[194] The third, troglitazone, was withdrawn from use because of its association with severe hepatic toxicity[195] (Table 5).

Mechanism of action

Thiazolidinediones are selective agonists for nuclear peroxisome proliferator-activated receptor-gamma (PPAR?).[196] The PPAR? are a family of nuclear receptors consisting of three subtypes designated PPARa, PPAR? and PPARd or –ß.[197] PPAR? receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle and liver. There is strong evidence to indicate that these receptors may be important regulators of adipose differentiation, lipid homeostasis, insulin action, and vascular endothelial function.[196,197] The TZDs bind to PPAR?, which, in turn, activate insulin-responsive genes that regulate carbohydrate and lipid metabolism. They require insulin to be present for their action. Thiazolidinediones exert their principal action by lowering insulin resistance in peripheral tissue, but an effect to lower glucose production by the liver has also been reported.[198,199] Thiazolidinediones increase glucose transport into muscle and adipose tissue by enhancing the synthesis and translocation of specific forms of the glucose transporter proteins.[196] The thiazolidinediones can also activate genes that regulate free fatty-acid (FFA) metabolism in peripheral tissue, thus lowering triglycerides and non-esterified fatty acid levels and inducing differentiation of adipocytes.[200]

Pharmacokinetics and pharmacodynamics

Rosiglitazone (Avandia) and pioglitazone (Actos) are taken once a day. Both are absorbed within 2 h, but the maximum clinical effect is not observed until after 6 to 12 weeks. Pioglitazone has a plasma half-life 3-7 h, reaching peak concentration about 2 h after administration. Rosiglitazone has a plasma half-life of 3-4 h and reaches peak plasma concentration after about an hour. Both drugs are highly (>99%) plasma protein bound. Both drugs undergo hepatic metabolism. Pioglitazone is metabolized, mainly by P450 isoforms CYP2C8 and CYP3A4, to active metabolites with a plasma half-life of 16-24 h. Rosiglitazone is metabolized, mainly by the P450 isoform CYP2C8 to weakly active metabolites with a plasma half-life of 100-150 h. Pioglitazone is excreted mainly in the bile, and rosiglitazone mainly in the urine.

Pioglitazone has beneficial effects on lipids; it increases high-density lipoprotein (HDL)-cholesterol and reduces triglycerides concentration, whereas rosiglitazone causes an increase in low-density lipoprotein (LDL)-cholesterol concentration.[201]

Regular monitoring of liver function should be carried out in patients receiving thiazolidinediones. These drugs can be administered to patients with renal insufficiency, but should not be used if there is active hepatic disease or if there are significant elevations of serum liver transaminases.

Contraindication

Thiazolidinediones are contraindicated in patients with a history of cardiac failure (New York Heart Association classes HV), severe renal insufficiency (rosiglitazone) or on dialysis (pioglitazone), combining with insulin (risk of heart failure), pregnancy, and breast-feeding.

Clinical use and adverse effects

Rosiglitazone, when used in combination with a sulfonylurea, is given at a dose of 4 mg/day, but this can be increased to 8 mg/day when used in combination with metformin. It is given once or twice a day, with or without food. The dose of pioglitazone is 15-30 mg/day, with or without food.

Pioglitazone and rosiglitazone are licensed for use as monotherapy in the USA, but only for combination therapy in Europe, either in combination with sulfonylureas in patients unable to tolerate metformin, or in combination with metformin. They are not licensed for use in combination with insulin (because both cause fluid retention), nor in children and pregnant women.

Liver function tests should be checked prior to initiation of therapy and then 2-monthly for the first year and periodically thereafter.

The main adverse effects are weight gain (dose-dependent) of 1-4kg after 6 months of treatment,[201] and fluid retention

that may be severe enough to exacerbate or precipitate heart failure.[202,203] The drugs also cause gastro-intestinal disturbances, anaemia, headache, visual disturbances, dizziness, haematuria, impotence; less commonly fatigue, insomnia, vertigo, hypoglycaemia and proteinuria. Though rosiglitazone has not been shown to be hepatotoxic in premarketing trials, a few case reports have implicated it as a cause of acute hepatocellular injury.[204]

Despite their effectiveness, rosiglitazone and pioglitazone remain second-line agents to metformin and glyburide, agents that have demonstrated efficacy in decreasing the microvascular and macrovascular complications associated with type 2 diabetes mellitus.

National Institution for Clinical Excellence (NICE) (UK) has advised (August 2003) that the use of a TZDs (pioglitazone or rosiglitazone) as second-line therapy added to either metformin or a sulfonylurea is not recommended except for:

- Patients who are unable to tolerate metformin and sulfonylurea combination therapy, or
- Patients in whom either metformin or a sulfonylurea is contra-indicated.

In such cases, the TZD should replace whichever drug in the combination is poorly tolerated or contra-indicated.

In conclusion, the introduction of the TZDs has heralded a new era in the treatment of patients with type 2 diabetes. These agents constitute a unique new class of oral antidiabetic agents that exert direct effects on the mechanisms of insulin resistance, which is the major pathophysiologic abnormality in type 2 diabetes. As mentioned earlier, they are highly selective and potent agonists for PPAR?, the TZDs regulate the expression of numerous genes that affect carbohydrate and lipid metabolism and vascular function. These results not only lower blood glucose levels and improved glycaemia, but also ameliorate several components of the insulin resistance syndrome, including dyslipidaemia, hypertension, and endothelial dysfunction, which lead to accelerated atherosclerosis and premature cardiovascular morbidity and mortality in patients with type 2 diabetes. Thus the TZDs have the potential not only to reduce glycaemia and insulin requirements in type 2 diabetics, but also improve other components of the insulin resistance syndrome including dislipidaemia and hypertension and thereby may be able to prevent or delay premature atherosclerotic cardiovascular disease, morbidity, and death.

Meglitinide analogues

The meglitinide analogues are a new class of drugs developed to improve early-phase insulin secretion, which is one of the earliest pathophysiologal manifestations of type 2 DM. These are derived from the meglitinide portion of sulfonylureas. Examples of this group are *repaglinide* and *nateglinide* (Table 5). Another meglitinide known as mitiglinide is undergoing clinical trials. Repaglinide is derived from the non-sulfonylurea moiety of glibenclamide whereas nateglinide is derived from the amino acid D-phenylalanine. The S-enantiomer of repaglinide is the pharmacologically active part of the racemic molecule. In the rat model, this enantiomer has more than 100 times greater hypoglycaemic potency than the R-enantiomer. Clinically available repaglinide is about 98% pure for the S-enantiomer. The meglitinides are rapid-acting insulin secretagogues (also known as prandial glucose regulators) that have a fast onset and short duration of action resulting in more physiological secretion of insulin from the ß-cell without causing continued elevation of insulin in the post-absorptive phase, thus reducing glycaemia without increasing the risk of hypoglycaemia. The mechanism of action of meglitinides is glucose-dependent and this has important implications for lessening the risk of hypoglycaemia.

Mechanism of action

The meglitinide analogues act on ß-cell receptors to stimulate insulin secretion by binding to the sulfonylurea receptor subunit and closing the K+ ATP channel,[205] but probably at a site distinct from that of the sulfonylurea receptor.[206] Closure of the potassium channel leads to depolarization of ß-cell plasma membrane, which promotes influx of calcium ions through voltage-gated calcium channels, resulting in exocytosis of insulin granules.

Repaglinide is five times more potent at stimulating insulin secretion than is glibenclamide. Repaglinide does not stimulate insulin secretion in the complete absence of glucose and its action is usually confined to intermediate concentrations of glucose. These properties account for the low risk of hypoglycaemia seen with repaglinide in contrast to the sulfonylureas. Nateglinide, from published studies, has been shown to have significantly faster association /dissociation kinetics in pancreatic ß-cell, which results in a more rapid and transient increase in early-phase insulin secretion in normal healthy volunteers compared to that with repaglinide.[205] Kinetic information from experiments on rat pancreatic cells has shown that time to 50% maximal inhibition was 4.1 min for nateglinide and 12 min for repaglinide. Time to 50% relief of inhibition was 35 min for nateglinide compared to 175 min for repaglinide. Additionally, in rat islet experiments have shown that there is 16-fold enhancement of nateglinide-induced inhibition of K+ATP current when the glucose concentration is raised from 3 to 16 mol/l. Repaglinide potency is increased four-fold whereas glibenclamide potency is reduced under the same condition. This explains the low incidence of mild and severe hypoglycaemia reported in clinical trials with nateglinide.

Pharmacokinetics

Repaglinide is rapidly absorbed, and peak plasma levels are reached within 30-60 min. Oral bioavailability is 65% and the plasma half-live is approximately 60 min in healthy volunteers and in patients with type 2 diabetes. These features of the drug allow for multiple preprandial use, as compared to the classical once- or twice-daily dosing of sulfonylureas. Repaglinide is primarily metabolized by the liver into inactive substances, and excreted predominately via the bile with about 6% being excreted via the kidney.[207]

Nateglinide is rapidly absorbed after oral administration and peak plasma levels are reached within 45 min.[208] Nateglinide is metabolized by the liver (85-90%); the metabolite is three to six times less potent in its activity than nateglinide. Nateglinide has 75% systemic bioavailability and is unaffected by first-pass hepatic metabolism. Only 10% is metabolized and excreted by the kidney. Nateglinide has a half-life of 1.5 h and 90% is bound to plasma proteins.

Uses and adverse effects

Residual ß-cell function is necessary for meglitinide analogues to be effective. Repaglinide is licensed as monotherapy in the treatment of patients with type 2 diabetes and may be used in combination with metformin when metformin alone is inadequate. The combination of metformin with repaglinide has been shown to be more effective than repaglinide or metformin monotherapy. [209] It may also be used in combination with thiazolidinediones. It is licensed for use in patients between the ages of 18 and 75 years. It is usually given 15-30 min before meals at a starting dose of 0.5 mg and if a meal is missed, the dose of repaglinide should also be omitted. The maximum single dose is 4 mg with a total daily dose of 16 mg.

Nateglinide also can be used in combination with metformin,[210] but it is not yet licensed as monotherapy. Nateglinide should initially be given at a dose of 60 mg three times a day before meals; this can be increase to 120 mg thrice daily and thence to 180 mg thrice daily.Repaglinide and nateglinide should be used cautiously in patients with hepatic insufficiency. They are contraindicated in severe hepatic impairment, pregnancy and breastfeeding.

The main adverse effect of meglitinide analogues is *hypoglycaemia.* Other adverse effects include *GIT disturbances, hypersensitivity* reactions including *pruritus, rashes* and *urticaria.*

a-Glucosidase inhibitors

a-Glucosidase inhibitors have been developed specifically to delay the digestion of complex carbohydrates and decrease the postprandial rise in plasma glucose, thus reproducing the effect of a low glycaemic index/high fiber diet (Table 5). These actions significantly reduce postprandial glycaemic and insulinaemic increase whether they are used as monotherapy or combined in the treatment of type 1 and type 2 diabetes. These drugs have an excellent safety profile.

Mechanism of action

a-Glucosidase inhibitors competitively block small intestine brush border enzymes that are necessary to hydrolyze oligo- and polysaccharides to monosaccharides. [211] Inhibition of this enzyme slows the absorption of carbohydrates; the postprandial rise in plasma glucose is blunted in both normal and diabetic subjects. [212]

Three a-glucosidase inhibitors have been developed: *acarbose, miglitol,* and *voglibose* and all have similar pharmacological profiles. Voglibose is currently only available in Japan and very little information is available with regards to its clinical trials.[213] Acarbose (Precose), an oligosaccharide of microbial origin, and miglitol (Glyset), a desoxynorjirimycin derivative, also competitively inhibit glucoamylase and sucrase but have weak effects on pancreatic a-amylase. Acarbose has an affinity of 10-100,000 times that of sucrose for a-Glucosidase. a-Glucosidase inhibitors reduce postprandial plasma glucose levels in T1DM and T2DM subjects. To be efficient, a-Glucosidase inhibitors must be present at the site of enzymatic action at the same time as the oligosaccharide or disaccharide. Therefore, they should be taken at the first bite and not more than 15 min after starting the meal.[214] a-Glucosidase inhibitors do not stimulate insulin release and therefore hypoglycaemia does not occur.

Pharmacokinetics

Acarbose is poorly absorbed (less than 2%) on oral administration and 35% of an oral dose appears as metabolites in the urine.[215] Miglitol is not metabolized and is excreted quantitatively by the kidney.[215] However, because of its close resemblance to the glucose molecule, miglitol is significantly absorbed through a jejunal transport mechanism identical to that of glucose.[215] It then circulates and concentrates in enterocytes of the small intestine. Acarbose is given initially at a dose of 25 mg at the start of a meal for 4-8 weeks followed by increase at 4- to 8-weeks interval up to 75 mg before each meal. This will reduce gastrointestinal side effects. Smaller doses are given with snacks. Acarbose is most effective when given with a starchy, high-fiber diet with restricted amounts of glucose and sucrose.[216]

Uses and adverse effects

a-Glucosidase inhibitors may be used as monotherapy in elderly patients or in patients with predominately postprandial hyperglycaemia. a-Glucosidase inhibitors typically are used in combination with other oral antidiabetic drugs and/or insulin. They should be given at the start of a meal. Studies have shown voglibose to be slightly less potent than acarbose, with no difference in gastrointestinal side effects.[213] When compared to sulfonylureas, a-glucosidase inhibitors appear to be less potent, with mean HbA_{1c} reduction of 0.85% versus 1.02% with sulfonylureas[217,218] In patients previously treated with sulfonylureas, acarbose seemed comparable to metformin for lowering HbA_{1c}.[219] The delay in carbohydrate digestion and their accumulation in the lower gastrointestinal tract increases the amount of fermentable carbohydrate reaching the colon. This results in dose-related flatulence, diarrhea, and abdominal bloating. This explains titrating the dose starting with smaller doses and increasing slowly over a period of 4- to 8-weeks. Lack of hypoglycaemia with a-glucosidase inhibitors is a major advantage.[212]

Treatment strategies for initiation of oral therapy

In patients with newly diagnosed type 2 diabetes in whom insulin therapy is not recommended:

- Initiate pharmacologic therapy with an oral agent preferably an insulin sensitizer. It is recommended to start with metformin, a thiazolidinedione, or a sulfonylurea as monotherapy as long as no contraindication is present. This view is based on

proven efficacy, safety and long-term clinical experience.[108,193] and is consistent with the guidelines of the ADA.[108,193] The meglitinides (repaglinide and nateglinide)[220] and the a-glucosidase inhibitors[221] are less effective than metformin/sulfonylureas/thiazolidinediones in reducing the HbA_{1c} level and are less commonly used, at least in the United States, to initiate therapy. If the blood glucose level is especially high (>280-300 mg/dl)(15.6-16.7 mM) and the patient is symptomatic, insulin should be considered as first-line therapy.

- If monotherapy with metformin, a thiazolidinedione, or a sulfonylurea fails to achieve the desired level of glycaemic control, a second oral agent should be added. Various combination tablets are available, including Metaglip (glipizide plus metformin), Glucovance (glyburide plus metformin) and Advandamet (rosiglitazone plus metformin).
- In diabetic patients in whom glycaemic control is not achieved with two oral agents, several options are available: 1) addition of a third oral agent; 2) addition of bedtime insulin to oral agent therapy; if this option is chosen, to avoid hypoglycaemia, it is preferred to stop sulfonylurea and continue the insulin sensitizer; 3) switching the patient to a mixed-split insulin regimen with or without an insulin sensitizer.

It is important to note that, ultimately, most patients with type 2 diabetes will require treatment with insulin, either alone or in combination with an oral agent.

Treatment of hypoglycaemia

- Initially glucose 10-20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps.
- Hypoglycaemia which causes unconsciousness is an emergency. *Glucagon* can be given for acute insulin-induced hypoglycaemia; it is not appropriate for chronic hypoglycaemia. It is given at a dose of 1 mg (1 unit) by intramuscular, subcutaneous and intravenous in circumstances when an intravenous glucose would be difficult or impossible to administer. If not effective within 10 min, give intravenous glucose.
- Alternatively, 50 ml of 20% glucose infusion may be given intravenously into a large vein through a large gauge needle. Care should be taken to see that it does not cause extravasation since it is an irritant at this concentration. Alternatively, 25 ml of 50% glucose intravenous infusion may be given, though this concentration is viscous and difficult to administer. Glucose at a concentration of 10 % can be given but a large volume is required.
- Hypoglycaemia caused by oral hypoglycaemic agents should be transferred to a hospital since the hypoglycaemic effects may persist for many hours.

Newer agents for the treatment of Diabetes mellitus

Potential new antidiabetic agents and compounds are undergoing clinical trials:

- *a-Glucosidase* inhibitors such as *voglibose* have already been mentioned earlier. It reduces the postprandial increase in glycaemia similar to acarbose and miglitol.
- *a-Amylase* inhibitors like acarbose are weak inhibitors of a-amylase activity, but attempts to specifically inhibit a-amylase activity have not been successful.
- Novel insulins. *Thyroxyl-insulin*, an insulin linked to thyroxine, is highly bound to plasma proteins via its thyroxyl moiety, ensuring a prolonged plasma half-life and limited transport across the endothelium, but has free access to hepatocytes. Others like insulin initiators and potentiators act by enhancing the effect of glucose and other nutrient initiators for example agents that increase cellular concentration of cyclic adenosine monophosphate (cAMP).
- A lot of attention has recently been focused on the therapeutic potential of glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP).[222] In the presence of stimulatory concentration of glucose, GLP-1 is a potent insulin secretagogue in non-diabetic subjects, subjects with impaired glucose tolerance (IGT), and type 2 diabetic subjects.[222] In acute and chronic studies, injection or infusion of GLP-1 before or during meals reduced postprandial hyperglycaemia and improved glycaemic control without causing clinical hypoglycaemia.[222] The main limitation to therapeutic application of GLP-1 has been its very short plasma half-life of less than two min after intravenous injection and 1 h after subcutaneous injection.[222] This is due to its rapid degradation at the N-terminal by the circulating enzyme dipeptidyl peptidase 4 (DPP-4).[222] Hence an analogue of GLP-1 that modify the amino acid sequence to avoid degradation has been developed; exendin-4 is such a product, that was first isolated from a North American Reptile known as the Gila monster (*Heloderma suspectum*). Exendin-4 has a longer half-life than native GLP-1, but retains the same biological profile.
- *GIP* stimulates insulin biosynthesis and contributes substantially to the overall incretin response, however, GIP may raise postprandial glucagon.
- *Dipeptidyl peptidase 4* (DPP-4) degrades a variety of circulating peptides (e.g. PYY and NPY) including glucagon, which might contribute to its glucose-lowering effect, but it is not yet evident whether the effects of DPP-4 inhibitors on other peptides could limit their use.

- Inhibition of *phosphodiesterase* (PDE) activity in islet ß-cells offers a potentially therapeutic approach to raise intracellular cAMP and thereby increase insulin biosynthesis and secretion. Several PDEs are expressed by pancreatic islet cells (PDE-1 to –5), and PDE-1, -3 and -5 appear to be the main types in ß-cells. Isoform PDE-3ß is mainly responsible for increasing glucose-induced insulin secretion and the challenge is to specifically target the ß-cells *in vivo* with a PDE-3ß inhibitor.
- *a-adrenoreceptors* in the ß-cell membrane normally mediate tonic suppression of insulin secretion, and in theory selective antagonist of these receptors should lift this suppression. However, potent and specific agents from the pharmaceutical industry has not yet emerged. The antibiotic *erythromycin* potentiates glucose-induced insulin release and might serve as a template for an antidiabetic drug. The neuropeptide pituitary adenylate-cyclase-activating polypeptide (PACAP) stimulates insulin secretion in a glucose-dependent manner, might be pharmacologically exploitable.[223]
- *Minerals*: *Magnesium, chromium* and *zinc* are often reduced in diabetics, and supplementation may improve glycaemic control in cases of mineral deficiency.[224] Hypomagnesium is not uncommon in insulin resistant states, and magnesium supplementation have improved insulin action and ß-cell function, and possibly reduce cardiovascular mortality in magnesium deficient diabetic patients.[224] Chromium deficiency is common in type 2 diabetes, especially the elderly, and chromium supplementation have improved glycaemic control, without increasing insulin concentrations.[225] Adequate chromium is necessary for normal insulin sensitivity, but the site of action of chromium is unresolved. Therapeutic indication for zinc supplements is not clear but high concentration of zinc can exe rt various insulin-like effects *in vitro* and *in vivo*, but the mechanisms are not established. However, zinc has been reported to protect against ß-cell damage and to improve glycaemic control in diabetic patients with liver disease.[226]
- *Vanadium salts* exert insulin-like effects on glucose metabolism *in vitro* and lower blood glucose levels in animal models of hyperinsulinaemic and hypoinsulinaemic animal models of diabetes.[227] Vanadium can improve glycaemic control in type 1 and type 2 diabetic patients, reduce insulin requirements and increase peripheral glucose utilization in type 2 diabetes. Additionally it enhances glucose transport in skeletal muscle suggesting an effect at a more distal step in the control of glucose transport. Though cellular accumulation and potential toxicity should be borne in mind, the high potent effects of peroxovanadium salts could enable use of very small doses of vanadium. Poor intestinal absorption of vanadium compounds could be addressed by organic vanadium complexes.
- Others are *vitamins* such as *niacin, thiamine* which facilitates glucose metabolism, and natural antioxidants like *vitamin C, vitamin E* (a-tocopherol), and *ß-carotene* have given equivocal results with regard to glycaemic control.
- *Aldose Reductase inhibitors* include *Epalrestat* and *Sorbinil*. These drugs inhibit the enzyme aldose reductase which catalyzes the conversion of glucose to sorbitol. Aldose reductase inhibitors have no influence on blood-glucose concentrations. They are given in diabetic complications including neuropathy.

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